

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Axel ULLRICH *et al.*
Title: NOVEL MEGAKARYOCYTIC
PROTEIN TYROSINE KINASES
Appl. No.: 09/977,260
Filing Date: 10/16/2001
Examiner: Seharaseyon, Jegatheesan
Art Unit: 1647

RECEIVED
MAR 09 2004

DECLARATION UNDER 37 C.F.R. § 1.131

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

1. I, Ricardo Martinez, am a Principle Senior Scientist at Pfizer, Inc., 10777 Science Center Drive, San Diego, CA, 92121.
2. I was previously employed as a research scientist at Sugen, Inc., 230 East Grand Avenue, South San Francisco, CA 94080-4811.
3. During my employment with Sugen, I sequenced the megakaryocytic protein tyrosine kinase, which is designated as "MKK1" in the present application, U.S. serial no. 09/977,260.
4. This declaration establishes that I obtained the DNA and amino acid sequences of the claimed MKK1 before the publication date of Bennett *et al.*, *J. Biol. Chem.*, 269(2), pp. 1068-74, January 14, 1994 ("the critical date").
5. I understand that the examiner of the present application rejected claims 1 and 7 as anticipated under 35 U.S.C. § 102(a) by either Bennett *et al.*, *supra*, or Sakano *et al.*, *Oncogene*, 9(4), pp. 1155-61, April, 1994 (Office Action dated October 2, 2003).
6. By "anticipated" I understand the examiner to assert that "the similarity of the DNAs (99.2%-99.7%) and the description of the proteins of the cited

references appears to indicate that these DNAs encode the MKK1 protein of the instant invention with greater than 99% identity” and that, therefore, “the disclosure of Bennett *et al.* or Sakano *et al.*, anticipates claims 1 and 7” (Office Action at page 9).

7. The DNA and amino acid sequences for the presently claimed MKK1 are depicted in the present application by the sequence identifiers SEQ ID NO. 1 and SEQ ID NO. 2, respectively.

8. Prior to the critical date, I determined the DNA and amino acid sequences for MKK1. See Appendix A (appended), which is a copy of 12 pages of my lab notebook.

9. The designation, “MKK1-3,” in the sequence information depicted in Appendix A refers to the third clone of MKK1 that was used for sequencing.

10. The term “consensus” in the header of the sequences depicted in Appendix A, refers to the collation of multiple short MKK1 sequences that were aligned by computer sequencing software to produce the full-length MKK1 DNA sequence. These shorter sequences were obtained from a number of “primer walking” sequencing runs of the third clone for MKK1 (“MKK1-3”).

11. Depicted in Appendix A is the sense and antisense nucleotide sequence for the clone MKK1-3, which spans 2053 nucleotides. The nucleotide region of the MKK1-3 clone sequence that encodes the MKK1 protein begins at nucleotide 253 (“C”). C₂₅₃ is the start of the nucleotide codon, C₂₅₃G₂₅₄A₂₅₅, which encodes the N-terminal arginine (“R”) residue of MKK1.

12. The nucleotide region of the MKK1-3 clone sequence that encodes the MKK1 protein ends at nucleotide 1764 (“C”), which is the 3’-nucleotide of the codon “C₁₇₆₂C₁₇₆₃C₁₇₆₄” that encodes proline (“P”) the C-terminal residue of MKK1.

13. The coding sequence of MKK1 is depicted in three reading frames in Appendix A. The N-terminal arginine encoded by C₂₅₃G₂₅₄A₂₅₅ begins on the second page of the Appendix and in the first reading frame. The C-terminal proline encoded by “C₁₇₆₂C₁₇₆₃C₁₇₆₄” is found on the eleventh page of Appendix A.

14. In this respect, the amino acid sequence for MKK1 is depicted in the first reading frame sequence until the tenth page of the Appendix. There is a frameshift, *i.e.*, the amino acid sequence corresponding to MKK1 of SEQ ID NO. 2 jumps from the first reading frame to the second reading frame and back again, between the region encoded by nucleotides 1580-1590. There is another frameshift between nucleotides 1640-1715.

15. Frameshifts were, and still are, commonplace in manual and automated sequencing runs. The quality of the DNA that is being read, the purity of the DNA preparation, and the integrity of the individual sequencing reactions can create, in places, ambiguous sequencing bands and artifacts on a sequencing gel.

16. I also am aware of an amino acid difference between the MKK1 amino acid sequence and SEQ ID NO. 2 of the present application: the codon spanning nucleotides 1552 ("C"), 1553 ("T"), and 1554 ("G") on the tenth page of Appendix A encodes a leucine ("L") amino acid. The corresponding codon in SEQ ID NO. 2 of the application, however, at nucleotides 1565 ("G"), 1566 ("T"), and 1567 ("G") encodes a valine ("V"). Accordingly, the single nucleotide difference, a "C" versus a "G," is the cause for this discrepancy in amino acid sequence.

17. I also note that the region spanning nucleotides 980-990, on the fifth page of Appendix A, contains two "Y" bases at positions 986 (codon, G₉₈₅Y₉₈₆T₉₈₇) and 989 (codon, G₉₈₈Y₉₈₉C₉₉₀). A "Y" nucleotide refers to either a cytosine ("C") or thymine ("T") under standard nucleotide nomenclature. Indeed, replacing Y₉₈₆ with a "C" and Y₉₈₉ with a "T" creates the correct amino acid residues, alanine and threonine, that should be depicted by these two codons.

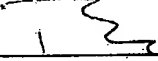
18. I believe that a sequencing artifact is an explanation for the nucleotide differences between my lab notebook sequence depicted in Appendix A and that of SEQ ID NO. 2 depicted in the present application. With respect to a sequencing artifact, it is very possible that band intensity and/or band compression on the autoradiogram used to read the four-lane sequencing reactions of the MKK1-3 clone, produced an ambiguous arrangement of bands at this position. It is not unusual for an autoradiogram to depict band intensities in more than one lane of a manual sequencing gel, particularly so with "C" and "G" nucleotides. Furthermore, depending on the degree of separation of those bands it can be difficult to accurately discern the correct band from a visual reading.

19. I attest that the MKK1 DNA and amino acid sequences were isolated and obtained before the publication of the Bennett *et al.* reference.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declarant:

Full name of declarant: Ricardo Martinez

Declarant's signature  Date 3/2/04

Country of Citizenship U.S.A

Residence and Post Office Address: 12658 Torrey Bluff Drive, Apt. #275,
San Diego, CA, 92130

PROJECT _____

Map Draw Indian of old

Page 1

MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

Enzymes: All 335 enzymes (No Filter)

Settings: Linear, Certain Sites Only, Standard Genetic Code

GTGCAGCGGGACGCTCGGGTGTGCAGCCGGCTCGCGGAGGCCTCCTGGGGGGGGSGCSCGGGCGCGGCT 70
CACGTGCGCCTGCGAGCCACACGTGCGCCGAGCGCCTCCGGAGGACCCCCCCCCSCGSGCCCCGCGCCGA

Only once

Below

SUG#301

SUG#313

V Q R D A R V C S R L A E A S W G G ? ? G R G
C S G T L G C A A G S R R P P G G G ? ? G A A
C A A G R S G V O P A R G G L L G G G A R A R L

CGGGGGCGCCCCYTRAGCAGAAAACAGGRAGAACCAGGCTSGGTCHAGTGGCACCMAGCTCCCTACYTCY 140
GCCCCGCGGGGRAYTCGTCTTTTGTCCYTCTTGGTCCGASCCAGKTCACCGTGGKTCGAGGGATGRAGR

Below

SUG#301

SUG#313

S G A P ? ? Q K T G R T R L G ? V A P S S L ? ?
R G R P L S R K O ? E P G ? V ? W H ? A P Y ?
G G A P . A E N R ? N Q A ? S S G T ? L P T S

KGTGCMAGCCGCTKGCTGTGGCAGGCCAWTCCCARCGKYCCCGACTGTGACCACTTGCTCAGTGTGCC 210
MCACGKTCGGCGGAMCGGACACCGTCCGGTWAGGGTYGCMRGGCTGACACTGGTGAACGAGTCACACGG

Below

SUG#301

SUG#313

V ? A A ? P V A G ? S Q R ? R L . P L A O C A
? C ? P P ? L W O A ? P ? ? P D C D H L L S V P
? A S R L A C G R P ? P ? ? P T V T T C S V C

Read and Understood By

RSC hlt
Signed

Date

mef
Signed

Date

001296

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PROJECT

MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

TCTCACSDGYCYCAKTTTCCCTCTGKGGGGCGATAGCGSGGCGAGGCTCTCTGGTTTCTGGCGGGCAT 280
AGAGTGSHERGRGTAAAGGGAGACNCCCCGCTATCCGSCCGCTCCGAGAGACCAAAGGACCGCCCGTA

Below

SUG#301

SUG#313

SUG#304

SUG#304

S H ? ? ? F P S ? G R A ? R G S L V S W R A
L T ? ? ? F P L ? G D R R G E A L W F P G G H
L S ? ? ? ? S L ? G A I G ? A R L S G F L A G I

TTCACGGCTGTGATTCTGCTGAGGAACCTCCCCGGGTGAGCCCCGCTTCTCCGAGCCTGGCACCCCCC 350
AAGTGCCGACACTAAGACGACTCCTTGAAGGGGCCACTCGGGGGCGAAGGAGGCTCGGACCGTGGGGGG

One strand

SUG#313

SUG#313

SUG#304

SUG#304

F H G C D S A E E L P R V S P R F L R A W H P P
F T A V I L L R N F P G A P A S S E P G T P
S R L F C G T S P G E P P L P P S L A P P

TCCCGTCTCAGCCAGGATGCCAACGAGGCGCTGGGCCCCGGGCACCCAGTGTATCACCAAATGCGAGCAC 420
AGGGCAGAGTCGGTCTACGGTTGCTCCGCGACCCGGGGCCCGTGGGTACATAGTGGTTTACGCTCGTG

One strand

SUG#313

SUG#313

SUG#304

SUG#304

SUG#301

P V S A R N P T R R W A P G T O C I T K C E H
L P S O P G C O R G A G P R A P S V S P N A S T
S R L S O D A N E A L G P G H P V Y H O H R A

RR Mr

highlighted residues show identical residues but in human
Cyt. (P.2)

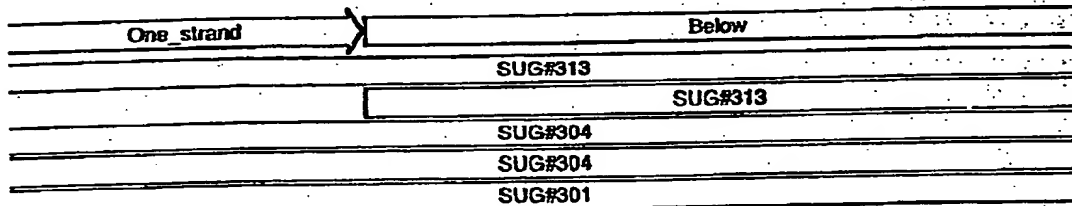
m. [signature]

PRO

MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

ACCCGCCCCAAGCCAGGGGAGCTGGCCTTCCGCAAGGGGCGACGTGGTCACCATCCTGGAGGCCTGCGAGA
TGGGCGGGGTTCCGGTCCCCCTCGACCGGAAGGCGTTCCCGCTGCACCAAGTGGTAGGACCTCCGGACGCTCT

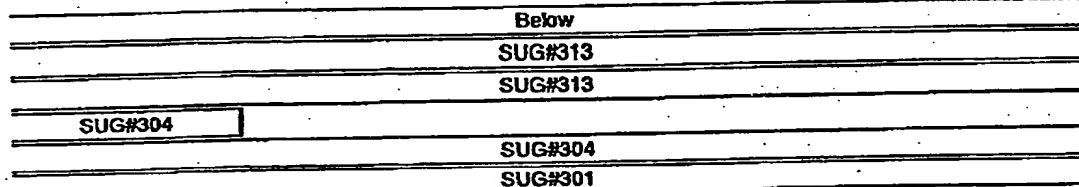
490



T R P K P G E L A F R K G D V V T I L E A C E
P A P S O G S W P S A R A T W S P S W R P A R
H P P Q A R G A G L P Q G R R G H P G G L R E

ACAAGAGCTGGTACCGCGTCAAGCACCACACCAAGTGGACAGGAGGGGCTGCTGGCAGCTGGGGCGCTGGC
TGTTCTCGACCATGGCGCAGTTCTGTGGTGTGGTCACTGTCTCTCCCGACGACCGTCGACCCCGCGACGC

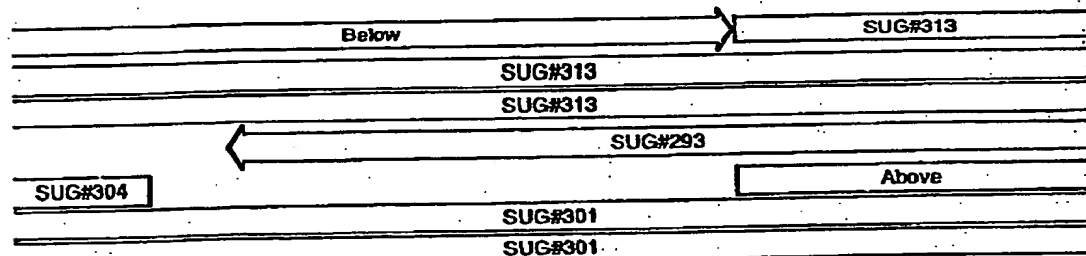
560



N K S W Y R V K H H T S G Q E G L L A A G A L R
T R A G T A S S T T P V D R R G C W O L G R C
Q E L V P R Q A P H Q W T G G A A G S W G A A

GGAGCGGGAGGCCCTCTCCGCGAGACCCCAAGCTCAGCCTCATGCCGTGGTTCCACGGGAAGATCTCGGGC
CCTCGCCCTCCGGGAGAGGCGTCTGGGGTTCGAGTCGGAGTACGGCACCAAGGTGCCCTTCTAGAGCCCG

630



E R E A L S A D P K L S L H P W F H G K I S G
G S G R P S P O T P S S A S C R G S T G R S R A

Signed

Date

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Date

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MKK1-3, consensus 4/12 Map (1 > 2053) Site and Sequence

G G G P L R R P O A O P H A V V P R E D L G

CAGGAGGCTGTCCAGCAGCTGCAGCCTCCCGAGGATGGGCTGTTCTGGTGCGGGAGTCCGCGCGCCACC 700
GTCCTCCGACAGGTCGTGACGTCGGAGGGCTCCTACCCGACAAGGACCACGCCCTCAGGCGCGCGGTGG

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SUG#293

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SUG#301

SUG#301

SUG#313

SUG#293

O E A V O O L O P P E D G L F L V R E S A R H
R R L S S S C S L P R N G C S W C G S P R A T
P G G C P A A A S R G W A V P G A G V R A P PCCGGCGACTACGTCCTGTGCGTGAGCTTTGGCCGCGACGTCATCCACTACCGCGTGCTGCACCGCGACGG 770
GGCCGCTGATGCAGGACACGCACTCGAAACCGGCGCTGCAGTAGGTGATGGCGCACGACGTGGCGCTGCC

SUG#313

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SUG#293

P G D Y V L C V S F G R D V I H Y R V L H R D G
P A T T S C A A L A A T S S T T A C C T A T
R R L R P V R E L W P R R H P L P R A A P R R

KR M (Signed)

LWC

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PRO

Page 5

7

MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

CCACCTCACAATCGATGAGGCCGTGTTCTTCTGCAACCTCATGGACATGGTGGAGCATTACAGCAAGGAC
GGTGGAGTGTTAGCTACTCCGGCACAAGAAGACGTTGGAGTACCTGTACCACCTCGTAATGTCGTTCTCG

840

SUG#313

SUG#313

SUG#313

SUG#293

Above

SUG#313

SUG#313

SUG#293

H L T I D E A V F F C N L M D H V E H Y S K D
A T S Q S M R P C S S A T S W T W W S I T A R T
P P H N R G R V L L O P H G H G G A L O O G

AAGGGCGCTATCTGCACCAAGCTGGTGAGACCAAAGCGGAAACACGGGACCAAGTCGGCCGAGGAGGAGC
TTCCCGCGATAGACGTGGTTCGACCACTCTGGTTTCGCCTTTGTGCCCTGGTTCAGCCGGCTCCTCCTCG

910

SUG#313

SUG#313

SUG#313

SUG#293

Above

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SUG#313

SUG#293

K G A I C T K L V R P K R K H G T K S A E E E
R A L S A P S W D O S G N T G P S R P R R S
O G R Y L H Q A G E T K A E T R D O V G R G G A

TGGCCAGGGCGGGCTGGTTACTGAACCTGCAGCATTTGACATTGGGAGCACAGATCGGAGAGGGAGAGTT
ACCGGTCCCGCCCGACCAATGACTTGGACGTCGTAACCTGTAACCCTCGTGTCTAGCCTCTCCTCTCAA

980

SUG#313

SUG#313

SUG#313

SUG#282

SUG#293

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MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

SUG#293

L A R A G W L L N L O H L T L G A O I G E G E F
W P G R A G Y T C S I H W E H R S E R E S
G O G G L V T E P A A F D I G S T D R R G R V

TGGAGYTGCCCTGCAGGGTGAGTACCTGGGGCAAAGGTGGCCGTGAAGAATATCAAGTGTGATGKACA 1050
ACCTCRACRGACGTCCCACTCATGGACCCCGTTTCCACCGGCACTTCTTATAGTTCACACTACANTGT

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SUG#313

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SUG#301

(Include me next page)
② ? ? L O G E Y L G O K V A V K N I K C D V T
L E L ? C R V S T W G K R W P R I S S V M ? O
W S C P A G V P G A K G G R E E Y O V C ?

CCCCAGGCCCTTCTGGACGAGACGGCCGTATGACGAAGATGCAACACGAGAACCTGGTGCGTCTCCTGG 1120
CGGGTCCGGAAGGACCTGCTCTGCCGGCAGTACTGCTTCTACGTTGTGCTCTTGGACCACGCAGAGGACC

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SUG#313

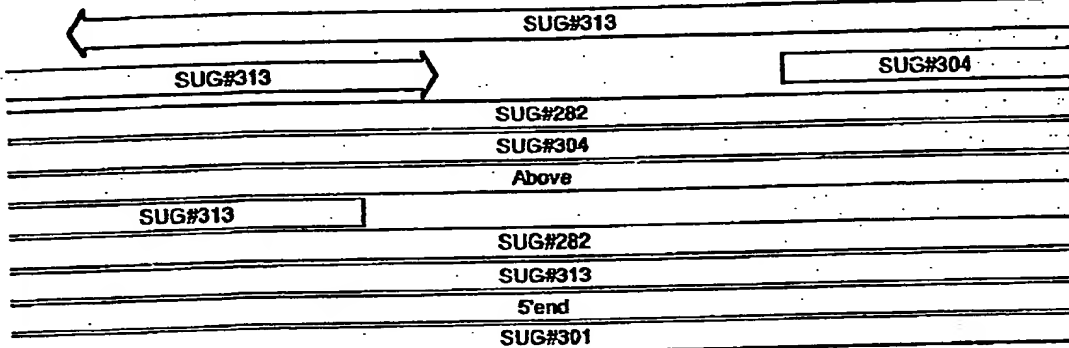
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SUG#301

A O A F L D E T A V H T K H O H E N L V R L L
P R P S W T R R P S R R C N T R T W C V S W
S P G L P G R D G R H D E D A T R E P G A S P G

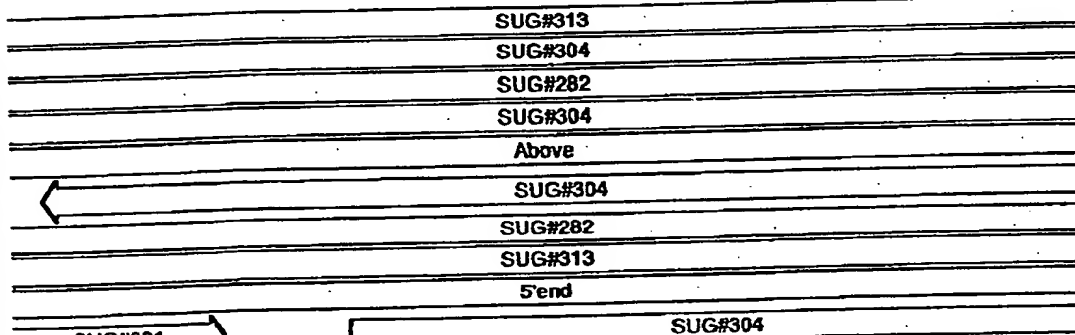
PR MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

GCGTGATCCTGCACCAGGGGCTGTACATTGTCATGGAGCACGTGAGCAAGGGCAACCTGGTGAACCTTCT 1190
 CGCACTAGGACGTGGTCCCCGACATGTAACAGTACCTCGTGCACCTCGTTCCCGTTGGACCACTTGAAAGA



G V I L H O G L Y I V M E H V S K G N L V N F L
 A S C T R G C T L S W S T A R A T W T F
 R D P A P G A V H C H G A R E Q G O P G E L S

GCGGACCCGGGGTGCAGCCCTCGTGAACACCGCTCAGCTCCTGCAGTTTTCTCTGCACGTGGCCGAGGGC 1260
 CGCCTGGGCCCCAGCTCGGGAGCACTTGTGGCGAGTCGAGGACGTCAAAGAGACGTGCACCGGCTCCCG



R T R G R A L V N T A O L L O F S L H V A E G
 C G P G V E P S T P L S S C S F L C T W P R A
 A D P G S S P R E H R S A P A V F S A R G R G

RZ mlu
 Signed

[Redacted]
 Date

mlet
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 Date

0 0 1 2 9 9

MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

ATGGAGTACCTGGAGAGCAAGAAGCTTGTGCACCGCGACCTGGCCGCCCGCAACATCCTGGTCTCAGAGG 1330
TACCTCATGGACCTCTCGTTCTTGAACACGTGGCGCTGGACCGCGGGCGTTGTAGGACCAGAGTCTCC

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SUG#282

SUG#313

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SUG#304

SUG#304

MKK-1

M E Y L E S K K L V H R D L A A R N I L V S E
W S T W R A R S L C T A T W P P A T S W S O R
H G V P G E O E A C A P R P G R P O H P G L R G

ACCTGGTGGCCAAGGTCAGCGACTTTGGCCTGGCCAAAGCCGAGCGGAAGGGGCTAGACTCAAGCCGGCT 1400
TGGACCACCGGTTCCAGTCGCTGAAACCGGACCGGTTTCGGCTCGCCTTCCCCGATCTGAGTTCGGCCGA

SUG#313

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SUG#304

Above

SUG#304

SUG#282

SUG#313

SUG#282

SUG#304

SUG#304

MKK-1

D L V A K V S D F G L A K A E R K G L D S S R L
T W W P R S A T L A W P K P S G R G . T O A G
P G G O G O R L W P G O S R A E G A R L K P A

R. R. M. H.
Signed

Date

Signed

Date

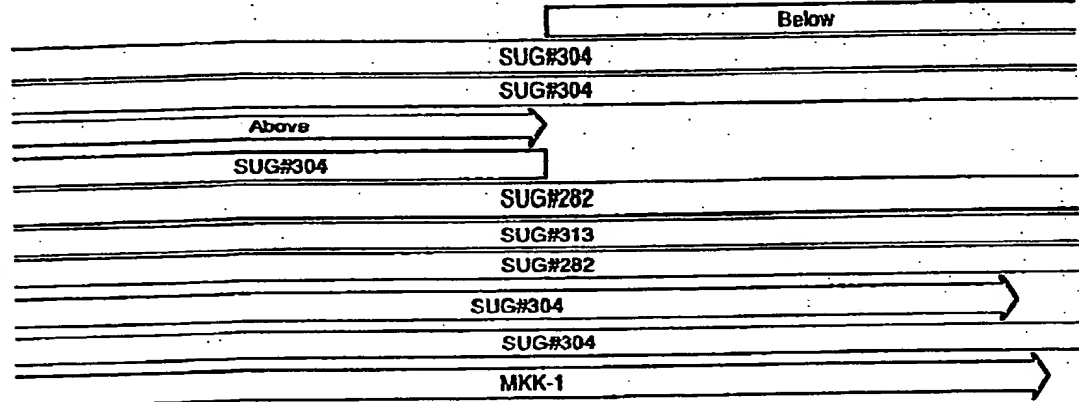
PRC

MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

G C C C G T C A A G T G G A C G G C G C C C G A G G C T C T C A A A C A C G G G A A G T T C A C C A G G A A G T C G G A T G T C T G G A G T

C G G G C A G T T C A C C T G C C G C G G G C T C C G A G A G T T T G T G C C C T T C A A G T G G T C G T T C A G C C T A C A G A C C T C A

1470

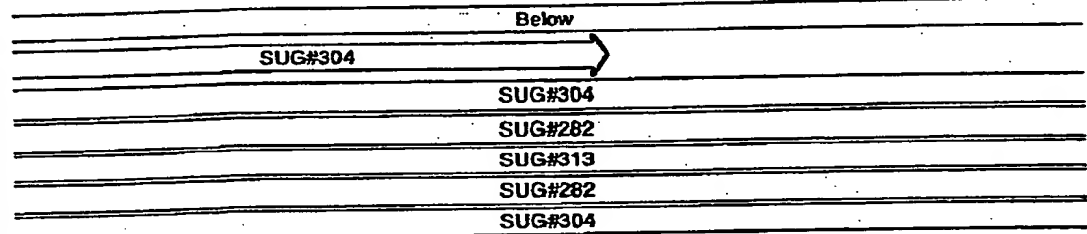


P V K W T A P E A L K H G K F T S K S D V W S
C P S S G R R P R L S N T G S S P A S R M S G V
A R O V D G A R G S O T R E V H Q Q V G C L E

T T T G G G G T G C T G C T C T G G G A G G T C T T C T C A T A T G G A C G G G C T C C G T A C C C T A A A A T G T C A C T G A A A G A G G

A A A C C C C A C G A C G A G A C C C T C C A G A A G A G T A T A C C T G C C C G A G G C A T G G G A T T T T A C A G T G A C T T T C T C C

1540



F G V L L W E V F S Y G R A P Y P K M S L K E
L G C C S G R S S H M D G L R T L K C H K R
F W G A A L G G L L I W T G S V P N V T E R G

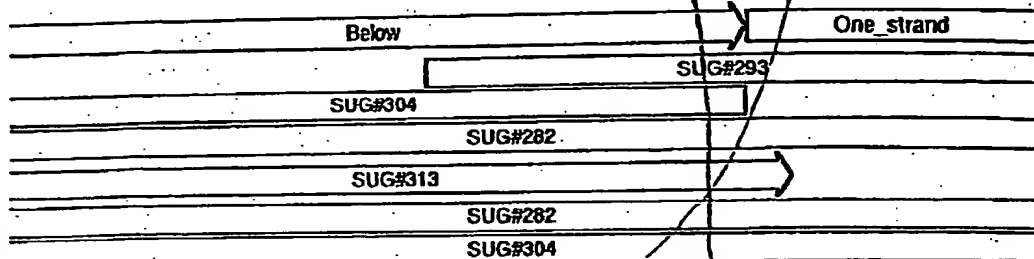
Rr *htr*
Signed

mfe
Signed

Possible ORF change
Terminator for ORF in final
3000 later (see P. 23)

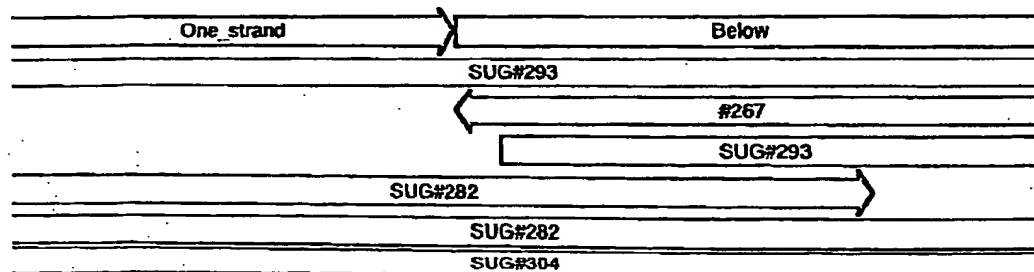
MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

TGTCGGAGGCCCTGGACAAGGGGTACCGCATGGAACCCCGAGGGCTGTCCAGGCCCGTGCACGTACT
ACAGCCTCCGGGACCTCTTCCCCATGGCGTACCTTGGGGGGGCTCCCGACAGGTCCGGGCACGTGCATGA 1610



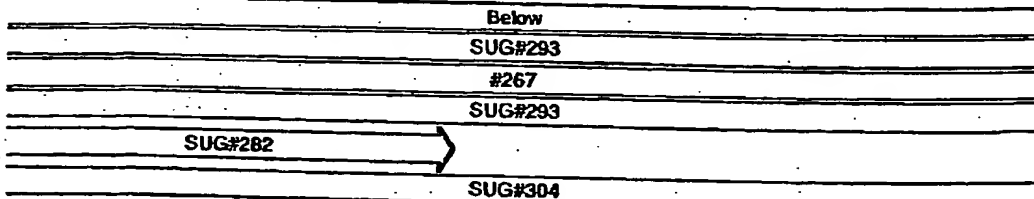
V S E A L E K G Y R H E P P R G S R P V H V L
C R R P W R R G T A W N P P E G C P G P C T Y
V G G P G E G V P H G T P P R A V O A R A R T

CATGAGCAGCTGCTGGGAGGCAGAGCCCGCCGGCCACCCTTCCGCAAACTGGCCGAGAAGCTGGCCC
GTACTCGTCGACGACCCTCCGTCTCGGGGGGGCCGGTGGGAAGGCGTTTGACCGGCTCTTCGACCGGG 1680



H S S C W E A E P A A G H P S A N W P R S W P
S A A A G R Q S P P P A T L P O T G R E A G P
H E O L L G G R A R R R P P F R K L A E K L A

GGGAGCTACGCAGTGCAGGTGCCCCAGCCTCCGTTCTCAGGGCAGGACGCCGACGGCTCCACCTCGCCCC
CCCTCGATGCGTCACGTCCACGGGGTCCGAGGCAAGAGTCCCGTCTGCGGCTGCCGAGGTGGAGCGGGG 1750



G S Y A V O V P O P P F S G O D A D G S T S P
G A T O C R C P S L R S O G R T P T A P P R P

rem

MP

PRC MKK1-3 consensus 4/12 Map (1 > 2053) Site and Sequence

R E L R S A G A P A S V L R A G R R R L H L A P

GAAGCCAGGAGCCCTGACCCACCCGGTGGGGCCCTTGGCCCAGAGGACCGAGAGAGTGGAGAGTACGGC
CTTCGGTCTCGGGACTGGGGTGGGCCACCCCGGAACCGGGTCTCTGGCTCTCTCACCTCTCATGCCG

1820

Below

SUG#293

#267

SUG#293

SUG#304

R S D E P P H P V G P L A O R T E R V E S T A
E A R S P D P T R W G P W P R G P R E W R V R
K P G A L T P P G G A L G P E D R E S G E Y G

GTGGGGGCACTGACCAGGCCCAAGGAGGGTCCAGGCGGGCAAGTCATCCTCTGGTGGCCACAGCAGGGG
CACCCCGTGACTGGTCCGGGTCTCTCCAGGTCCGCCCGTTCAGTAGGAGGACCACGGGTGTCGTCCCC

1890

Below

SUG#293

#267

SUG#293

W G H P G P R R V O A G K S S S W C P O Q G
R G G T D O A G G S R R A S H P P G A H S R G
V G A L T R P K E G P G G O V I L L V P T A G

CTGGCCACGTAGGGGGCTCTGGGCGGGCCGTGGACACCCAGACCTGCGAAGGATGATCGCCCGATAAA
GACCGGSGCATCCCCGAGACCCGCCGGGCACCTGTGGGGTCTGGACGCTTCTACTAGCGGGCTATT

1960

Below

SUG#293

#267

SUG#293

L A H V G G S G R P V D T P D L R R M I A R
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A G P R R G L W A A R G H P R P A K D D R P I K

Rz Mr
signed

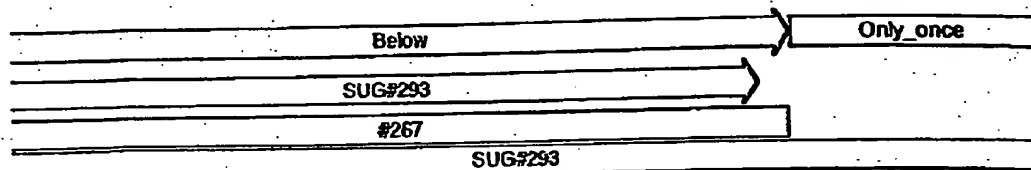
Date

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0 0 1 3 0 1

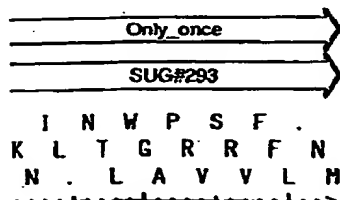
MKK1-3 consensus 4/12 Map (1-2053) Site and Sequence

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R R I L R T L K K G G A R Y P I R P I V S R I K
D G F G L K K G G P G T O F A L V V L
T D S K D S K K R G G P V P N S P Y S Y

AATTAAGTGGCCGTCGTTTTAAT
TTAATTGACCGGCAGCAAAATTA 2053



PR MR

mfet